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EXAMINER	
LIU, SUE XU	

ART UNIT	PAPER NUMBER
1639	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/532,258	JOUNG ET AL.	
	Examiner	Art Unit	
	SUE LIU	1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 January 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-95* is/are pending in the application.

4a) Of the above claim(s) *40-95* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-39* is/are rejected.

7)☒ Claim(s) *8* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☒ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *9/6/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claim Status

1. Claims 1-95 are currently pending.

Claims 40-95 have been withdrawn.

Claims 1-39 are being examined in this application.

Request for Interview

2. It appears that applicants have requested a telephone interview from the Examiner. Applicants request for an interview is granted. Please contact the examiner at the telephone number indicated below to arrange a mutually beneficial time.

Election/Restrictions

3. Applicant's election with traverse of Group 1 (claims 1-39) in the reply filed on 8/28/08 is acknowledged. The traversal is on the ground(s) that there is unity of invention among the various restricted groups. This is not found persuasive because the various of groups of inventions as set forth in the previous restriction requirement lack unity of invention. Applicants asset the various groups share "the same or a corresponding special technical feature", which the feature is the method recited in the instant claim 1.

Contrary to applicant's assertion, each group of invention has a different technical feature. First, under PCT Rule 13.2, "Unity of invention exists only when there is a technical relationship among the claimed inventions involving one or more special technical features. The

term "special technical features" is defined as meaning those technical features that define a contribution which each of the inventions considered as a whole, makes over the prior art." (MPEP 1850 I; emphasis added).

"Whether or not any particular technical feature makes a "contribution" over the prior art, and therefore constitutes a "special technical feature," should be considered with respect to novelty and inventive step. For example, a document discovered in the international search shows that there is a presumption of lack of novelty or inventive step in a main claim, so that there may be no technical relationship left over the prior art among the claimed inventions involving one or more of the same or corresponding special technical features, leaving two or more dependent claims without a single general inventive concept.

Lack of unity of invention may be directly evident "a priori," that is, before considering the claims in relation to any prior art, or may only become apparent "a posteriori," that is, after taking the prior art into consideration."

(MPEP 1850 II; emphasis added).

The MPEP also provide further guideline on determining lack of unity "a prior". See MPEP 1850 II. For example, independent claims "can be said to lack unity a priori as there is no subject matter common to all claims."

In the instant case, the technical feature for the Group 1 invention is a zinc finger polypeptide; the technical feature of Group 2 is a gene of interest; the technical feature of Group 3 is a fusion polypeptide; etc. Further, the Group 2 invention is a method of regulating the expression of a gene, using zinc finger polypeptides, and do not require the method steps of the instant claim 1. Similarly, the Group 3 invention is drawn to a zinc finger polypeptide, not a method, and thus also does not require the method steps of the instant claim 1. Therefore, Groups 1-7 are not so linked by the same or a corresponding special technical feature as to form a single inventive concept.

In addition, the special technical feature of Group 1 is known in the prior art. Wolfe et al (Structure. Vol. 8: 739-750; 6/21/2000; cited in IDS) teach combinatorial libraries of zinc finger

proteins derived from Zif268 (e.g. Abstract). The Wolfe reference also teaches selecting or screening for zinc finger proteins from a library of zinc finger proteins (e.g. Figures 4 and 5; pp.741+). In addition, Isalan et al (Nature Biotechnology. Vol.19: 656-660; 7/2001), throughout the publication, teach methods of generating recombinant zinc fingers based on selecting mutant zinc finger proteins that bind to a predetermined nucleic acid sequence. The Isalan reference also teach recombining two individually developed zinc finger protein libraries to generate secondary libraries (see more detailed discussion below under 35 USC 102(b)). Therefore, the inventions lack unity as demonstrated by showing the common technical feature(s) does not "define a contribution over the prior art" "*a posterior*". See MPEP 1850.

The requirement is still deemed proper and is therefore made FINAL.

4. Claims 40-95 have been withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected inventions, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 8/28/08.

5. Applicant's election of the following species:

A.) three zinc finger;

B.) Cys2His2;

in the reply filed on 8/28/08is acknowledged.

Priority

6. This application is filed under 35 U.S.C 371 of PCT/US03/34010 (filed on 10/23/2003), which claims priority to US provisional applications 60/420,458 (filed on 10/23/2002) and 60/466,889 (filed on 04/30/2003).

Information Disclosure Statement

7. The IDS filed on 9/6/2005 has been considered. See the attached PTO 1449 form.

Oath/Declaration

8. The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because:
It was not executed in accordance with either 37 CFR 1.66 or 1.68.

It appears that one of the listed inventors did not sign the Oath/Declaration.

Specification

9. The specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification. MPEP 608.01.

Claim Objections

10. Claim 8 us objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. The instant claim 8 is repeating the same limitation as recited in step a) of the instant claim 1.

Claim Rejections - 35 USC § 112

11. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

12. Claims 1-39 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claim language of the instant claim 1 is unclear and renders the said claim indefinite. First, Claim 1 is rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential structural cooperative relationships of elements, such omission amounting to a gap between the necessary structural connections. See MPEP § 2172.01. The omitted structural cooperative relationships are: the relationship between the element of "isolating pools comprising nucleic acid sequences" of step (b) and the various elements of step (a). It is not clear to what "pools" the instant claim language is referring. It is not clear if the "pools" are derived from the "libraries" of zinc finger polypeptides, or from different selection steps. The

relationship between the "pools comprising nucleic acid sequences" in step b) and the various elements of step a) of the instant claim 1 is also not clear.

The phrase "said polypeptides comprise the first binding complexes" in steps b) (as well as a similar recitation in step e)) is also confusion and unclear. In step a) of claim 1, the "first binding complexes" are formed between library members and the target site construct (i.e. a binding complex formed between a zinc finger polypeptide and a DNA target site). Thus, it is not clear how the zinc finger "polypeptides" can comprise "the first binding complexes" or how the "isolated nucleic acid sequences" encode for the "first binding complexes".

Claim Rejections - 35 USC § 102

13. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Isalan

14. Claims **1-14, 16-19, 21, 22, 27-29, 32, 34, 35** and **37** are rejected under **35 U.S.C. 102(b)** as being anticipated by **Isalan** et al. (Nature Biotechnology. Vol.19: 656-660; 7/2001).

The instant claims recite "A method of selecting a zinc finger polypeptide that binds to a sequence of interest comprising at least two subsites, said method comprising the steps of:

a) incubating position-sensitive primary libraries with target site constructs under conditions sufficient to form first binding complexes, wherein said primary libraries comprise zinc finger polypeptides having one variable finger and at least one anchor finger, and wherein

the target site construct has one subsite with a sequence identical to a subsite of the sequence of interest, and one or more subsites with sequences to which the anchor finger(s) bind;

b) isolating pools comprising nucleic acid sequences encoding polypeptides, wherein said polypeptides comprise the first binding complexes;

c) recombining the pools to produce a secondary library;

d) incubating the secondary library with the sequence of interest under conditions sufficient to form second binding complexes; and

e) isolating nucleic acid sequences encoding zinc finger polypeptides, wherein said polypeptides comprise the second binding complexes."

Claim interpretation: As discussed supra, the instant claim language (claim 1) is unclear and can be interpreted various. The relationships among the various claimed elements are not clear. The following discussion is in light of broadest and reasonably interpretation of the instant claims.

Isalan et al, throughout the publication, teach methods of generating recombinant zinc fingers based on selecting mutant zinc finger proteins that bind to a predetermined nucleic acid sequence (e.g. Abstract; pp.656+).

For **claim 1** step a): *incubating position-sensitive primary libraries with target site constructs under conditions sufficient to form first binding complexes, wherein said primary libraries comprise zinc finger polypeptides having one variable finger and at least one anchor finger, and wherein the target site construct has one subsite with a sequence identical to a subsite of the sequence of interest, and one or more subsites with sequences to which the anchor finger(s) bind:* This method step is interpreted to mean binding libraries of zinc finger containing proteins to nucleic acid target constructs containing "an anchor site" and a site with a

nucleic acid "sequence of interest" (or a predetermined nucleic acid sequence). The reference teaches generating libraries (at least two libraries) of randomized zinc finger proteins, where a wildtype finger is combined with two randomly mutated zinc fingers (e.g. Figure 1; pp.656-657), which the wildtype finger reads the "anchor finger" and the mutated fingers read on the "variable finger". The reference also teaches binding the said libraries of zinc finger proteins to a construct comprising a "predetermined DNA sequence" (e.g. p.657; Figure 2; Table 1 shows an example of using a HIV promoter sequence as the predetermined DNA sequence) and a segment of DNA sequence that binds to the wild-type zinc finger, which the predetermined DNA sequence reads on "a sequence of interest", and the wild-type zinc finger binding sequence reads on the "anchor finger" binding sequence. The instant specification broadly defines the term" position-sensitive" (e.g. Spec. p.6, lines 5+), which can be reasonably interpreted to be any zinc finger libraries that have multiple zinc finger domains (that may have interactions). The reference teaches the generated zinc fingers of the proteins interact with other to achieve "comprehensive DNA recognition" (e.g. p.657), which reads on the inherent property of "position-sensitive".

For **claim 1** step (b): *isolating pools comprising nucleic acid sequences encoding polypeptides, wherein said polypeptides comprise the first binding complexes:* As discussed above, it is not clear to which "pools" the instant claim is referring, the nexus between step (a) and (b) is also not clear, and the language of "said polypeptides comprise the first binding complexes" is also not clear. The instant claim 1 step (b) is interpreted to mean isolating nucleic acids (molecules) that encode for the zinc finger proteins that bind to the "target site constructs". The reference teaches isolating or selecting the polypeptides that bind to the target constructs

through, for example, phage display selection (e.g. Figure 1; p.657), which the selected phage would comprise the DNA encoding for the selected zinc finger polypeptides.

For **claim 1** step (c): *recombining the pools to produce a secondary library:* The reference teaches recombining the DNA sequences (encoding for the zinc finger polypeptides) of the selected two libraries of zinc fingers (e.g. Figure 1; p.657, left col.).

For **claim 1** step (d): *incubating the secondary library with the sequence of interest under conditions sufficient to form second binding complexes:* The reference also teaches binding the recombined zinc finger polypeptides with the predetermined sequence through additional rounds of selection (e.g. Figure 1; Table 1; pp.657-658).

For **claim 1** step (e): *isolating nucleic acid sequences encoding zinc finger polypeptides, wherein said polypeptides comprise the second binding complexes:* The claim language of step (e) is unclear as discussed supra. The reference teaches isolating nucleic acids (molecules) that encode for zinc finger proteins that bind to the predetermined sequence of interest (e.g. pp.657+; Figure 1).

For **claims 2** and **3**: The reference teaches at least two or three zinc fingers (e.g. Figures 1 and 2).

For **claim 4**: The reference teaches the target construct having the predefined sequence (or DNA sequence of interest) (e.g. Figure 2; Table 1).

For **claim 5**: The reference teaches various numbers base pairs (such as 3 bps) at the zinc finger binding DNA sequence (e.g. Figure 2 and Table 1).

For **claims 6** and **7**: The reference teaches various numbers (such as 3 sites for three fingers) of binding sites (e.g. Figure 2 and table 1).

For **claim 8**: The reference also teaches binding the said libraries of zinc finger proteins to a construct comprising a "predetermined DNA sequence" (e.g. p.657; Figure 2; Table 1 shows an example of using a HIV promoter sequence as the predetermined DNA sequence) and a segment of DNA sequence that binds to the wild-type zinc finger, which the predetermined DNA sequence reads on "a sequence of interest", and the wild-type zinc finger binding sequence reads on the "anchor finger" binding sequence.

For **claim 9**: The reference teaches the wild-type target site (the anchor finger binding sequence) comprises sequence of GCC (e.g. Figure 2A where the binding sequence for Lib23).

For **claims 10, 12-14** and **16-19**: The reference teaches the library of zinc finger proteins comprise wildtype finger sequence form a naturally occurring zinc finger protein, Zif268 (e.g. p.657) as well as phage displayed mutant Zif268 zinc finger proteins (e.g. Figure 1).

For **claim 11**: As the reference teaches the anchor fingers to be of the same structure as the instant claimed anchor finger (which is also derived from Zif268), the reference's teachings read on the inherent properties of low affinity and/or specificity.

For **claims 21** and **22**: The reference teaches randomizing at least the residues within the α-helical region of the zinc fingers (e.g. Figure 2).

For **claims 27, 28, 34** and **35**: The reference teaches expressing the zinc finger library in bacteriophage system (e.g. p.659).

For **claims 29** and **37**: The reference teaches incubating the phage displayed proteins with the target constructs in test tubes (i.e. in vitro) (e.g. p.660).

For **claim 32**: The reference teaches using PCR to recombine the two libraries of genes encoding for the zinc finger proteins. (e.g. p.660).

Claim Rejections - 35 USC § 103

15. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

16. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Isalan and Isalan II

17. Claims **1-14, 16-19, 21-25, 27-29, 32, 34, 35** and **37** are rejected under 35 U.S.C. 103(a) as being unpatentable over **Isalan** et al. (Nature Biotechnology. Vol.19: 656-660; 7/2001), in view of **Isalan** et al. (Biochemistry. Vol.37: 12026-12033; 1998; referred to as Isalan II).

Isalan et al teach methods of generating recombinant zinc fingers based on selecting mutant zinc finger proteins that bind to a predetermined nucleic acid sequence, as discussed supra. The teachings of the Isalan reference as discussed above is hereby incorporated by reference in its entirety.

Isalan et al do not explicitly teach between 16 to 20 amino acids are represented at each of the randomized positions as recited in **clms 23-25**.

However, **Isalan II**, throughout the publication, teach generating various zinc finger proteins using phage display technology (e.g. Abstract). The reference teaches randomizing the desired positions in the zinc finger region (e.g. p.12027). The reference also teaches generating codons for all 20 amino acid residues (e.g. p.12028, left col.). The reference also teaches the need to generate diverse amino acid sequence for the selection process (e.g. 12026).

Therefore, it would have been prima facie obvious for one of ordinary skill in the art at the time the invention was made to generate randomized zinc finger protein libraries comprising various number of possible amino acid residues at each randomized position.

A person of ordinary skill in the art would have been motivated at the time of the invention to represent the desired number of amino acids at each randomized positions in a zinc finger, because Isalan II teaches the need to generate randomized zinc finger proteins with diverse sequences and it is routine and known to generate libraries that represent various number of amino acids (such as all 20 amino acids). In addition, because both the Isalan references teach methods of generating randomized zinc finger libraries with random amino acid mutation at various positions within the α-recognition region for various screening purposes, it would have been obvious to one skilled in the art to substitute one set of amino acids (that are represented at each position; such as 8 different amino acids) for the another set (such as 16 to 20 amino acids) to achieve the predictable result of generating libraries of randomized zinc fingers representing various amino acids at the mutated positions.

A person of ordinary skill in the art would have reasonable expectation of success of achieving such modifications since all of the cited references have demonstrated the success of generating randomized zinc finger protein libraries with randomized positions representing the desired number amino acids.

Isalan and Others I

18. Claims **1-14, 16-19, 21-29, 32-35** and **37** are rejected under 35 U.S.C. 103(a) as being unpatentable over **Isalan** et al. (Nature Biotechnology. Vol.19: 656-660; 7/2001) and **Isalan** et al. (Biochemistry. Vol.37: 12026-12033; 1998; referred to as Isalan II), as applied to claims 1-14, 16-19, 21-25, 27-29, 32, 34, 35 and 37, and further in view of **Choo** et al. (WO 00/27878; 5/18/2000).

Isalan et al teach methods of generating recombinant zinc fingers based on selecting mutant zinc finger proteins that bind to a predetermined nucleic acid sequence, as discussed supra.

Isalan II, throughout the publication, teach generating various zinc finger proteins using phage display technology, as discussed supra.

The combined teachings of the Isalan and Isalan II references as discussed above are hereby incorporated by reference in their entirety.

The combination of the Isalan and Isalan II references does not explicitly teach the libraries of proteins are expressed in vitro as recited in **clms 26** and **33**.

However, **Choo** et al., throughout the publication, teaches various methods of generating mutant zinc finger protein libraries, and methods of screening the libraries (e.g. Abstract). The

reference teaches using in vitro polysome display of zinc finger proteins (e.g. p. 22; p.24), which the zinc finger polypeptides are produced in vitro using an in vitro transcription/translation system. The reference also teaches the in vitro protein production method offers various advantages such as improved affinity screening (e.g. p.23, lines 10+).

Therefore, it would have been prima facie obvious for one of ordinary skill in the art at the time the invention was made to generate mutant zinc finger proteins using in vitro expression.

A person of ordinary skill in the art would have been motivated at the time of the invention to use in vitro expression to produce mutant zinc finger proteins, because Choo et al. teach various advantages of in vitro expression such that a convenient and improved affinity screening methods can be used. In addition, because all of the cited references teach methods of producing mutant zinc finger proteins using various routine and known expression methods, it would have been obvious to one skilled in the art to substitute one expression method (in vivo production) for the other (in vitro production) to achieve the predictable result of expressing the desired zinc finger proteins.

A person of ordinary skill in the art would have reasonable expectation of success of achieving such modifications since all of the cited references have demonstrated the success of generating randomized/mutant zinc finger protein libraries using various protein production techniques.

Isalan and Others II

19. Claims **1-14, 16-19** and **21-39** are rejected under 35 U.S.C. 103(a) as being unpatentable over **Isalan** et al. (Nature Biotechnology. Vol.19: 656-660; 7/2001), Isalan et al. (Biochemistry. Vol.37: 12026-12033; 1998; referred to as **Isalan II**) and **Choo** et al. (WO 00/27878; 5/18/2000), as applied to claims 1-14, 16-19, 21-29, 32-35 and 37, and further in view of **Joung** et al. (PNAS. Vol.97: 7382-7387; 6/20/2000).

Isalan et al teach methods of generating recombinant zinc fingers based on selecting mutant zinc finger proteins that bind to a predetermined nucleic acid sequence, as discussed supra.

Isalan II, throughout the publication, teach generating various zinc finger proteins using phage display technology, as discussed supra.

Choo et al., throughout the publication, teaches various methods of generating mutant zinc finger protein libraries, and methods of screening the libraries, as discussed supra.

The combined teachings of the Isalan, Isalan II and Choo references as discussed above are hereby incorporated by reference in their entirety.

The combination of the Isalan, Isalan II and Choo references does not explicitly teach the libraries are incubated in cells as recited in **clms 30**, **31**, **38** and **39**. The reference also does not explicitly teach the incubation is performed under "high stringent condition" as recited in **clm 36**.

However, **Joung** et al., throughout the publication, teach methods of generating randomly mutated zinc finger proteins and screening the zinc finger target binding in cells (e.g. Abstract). The reference teaches using a bacterial two hybrid system for zinc finger selection (e.g. Abstract; pp.7383). The reference also teaches the advantages of using such a system so that zinc finger

proteins with high affinity can be isolated in a single selection step, and thus allowing a more rapid screening process (e.g. Abstract). The reference also teaches using various selection conditions to select for zinc finger proteins that bind to the target sites (e.g. pp.7383+). The reference also teaches the selection system used is under "stringent standard" and "account for why we isolated such a small number of specific candidates".

Therefore, it would have been prima facie obvious for one of ordinary skill in the art at the time the invention was made to screen for zinc finger polypeptides using an in vivo bacterial system and performing the selection process under high stringency.

A person of ordinary skill in the art would have been motivated at the time of the invention to using a bacterial cell based selection system to screen for target binding zinc finger proteins, because Joung et al. teach the advantages of using a bacteria call based system so that zinc finger proteins with high affinity can be isolated in a single selection step, and thus allowing a more rapid screening process. In addition, because all of the cited references teach methods of screening mutant/randomized zinc finger proteins for binding to nucleic acid targets of interest using various screening techniques, it would have been obvious to one skilled in the art to substitute one screening strategy (in vitro affinity assay) for the other (in vivo bacteria cell based 2 hybrid system) to achieve the predictable result of selecting for desired zinc finger proteins.

A person of ordinary skill in the art would have been motivated at the time of the invention to select zinc finger proteins under high stringency to obtain high affinity binding proteins, because Joung et al. teach the need to perform the selection under high stringency so that zinc finger proteins with high affinity and specificity can be obtained. Thus, it would have been obvious to one of ordinary skill in the art to apply the standard technique of

screening/selecting zinc finger proteins under various conditions, to improve and/or optimize the screening/selection assay for the predicable result of enabling standard protein selection that would result in desired proteins with the desired binding affinity/specificity for targets of interest.

A person of ordinary skill in the art would have reasonable expectation of success of achieving such modifications since all of the cited references have demonstrated the success of generating selecting various mutant/randomized zinc fingers using various protein production techniques under various conditions.

Isalan and Others III

20. Claims **1-39** are rejected under 35 U.S.C. 103(a) as being unpatentable over **Isalan** et al. (Nature Biotechnology. Vol.19: 656-660; 7/2001), Isalan et al. (Biochemistry. Vol.37: 12026-12033; 1998; referred to as **Isalan II**), **Choo** et al. (WO 00/27878; 5/18/2000) and **Joung** et al. (PNAS. Vol.97: 7382-7387; 6/20/2000), as applied to claims 11-14, 16-19 and 21-39, and further in view of **Chandrasegaran** (US 6,265,196; 7/24/2001).

Isalan et al teach methods of generating recombinant zinc fingers based on selecting mutant zinc finger proteins that bind to a predetermined nucleic acid sequence, as discussed supra.

Isalan II, throughout the publication, teach generating various zinc finger proteins using phage display technology, as discussed supra.

Choo et al., throughout the publication, teaches various methods of generating mutant zinc finger protein libraries, and methods of screening the libraries, as discussed supra.

Joung et al., throughout the publication, teach methods of generating randomly mutated zinc finger proteins and screening the zinc finger target binding in cells, as discussed supra.

The combined teachings of the Isalan, Isalan II, Choo and Joung references as discussed above are hereby incorporated by reference in their entirety.

The combination of the Isalan, Isalan II, Choo and Joung references does not explicitly teach the specific zinc finger sequence as recited in **clms 15** and **20**.

However, **Chandrasegaran**, throughout the patent, teach using various zinc finger protein with various amino acid sequences (e.g. Abstract). The reference specifically teaches using a zinc finger with amino acid sequence "QGGNLVR" for recognizing (or binding) the target sequence of GAA (e.g. col.22, Table 1), which the AA sequence matches SEQ ID NO:3. The reference also teaches designing zinc fingers with the appropriate amino acid sequence for binding to desired DNA target sequence of interest (e.g. col.16).

Therefore, it would have been prima facie obvious for one of ordinary skill in the art at the time the invention was made to generate zinc finger proteins comprising various amino acid sequences including sequences that are known to bind to certain target sites.

A person of ordinary skill in the art would have been motivated at the time of the invention to use generate zinc finger proteins to comprise a desired known sequence such as the sequence in SEQ ID NO:3, because Chandrasegaran teaches the sequence is known to bind to a specific target sequence and it is routine and known to alter the zinc finger sequences for binding to the desired target sites. In addition, because all of the cited references teach generating zinc finger proteins for binding to desired nucleic acid sequence of interest, it would have been obvious to one skilled in the art to substitute one known zinc finger sequence for the other to

achieve the predictable result of generating zinc finger polypeptide with the desired AA sequences.

A person of ordinary skill in the art would have reasonable expectation of success of achieving such modifications since all of the cited references have demonstrated the success of generating selecting various mutant/randomized zinc fingers using various protein production techniques under various conditions.

Double Patenting

21. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

'031

22. Claim 1 is provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 51 and 52 of copending Application No. 10/532,031 (PGPUB 20060246110). Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of the '031 application read on the instant claim 1.

The '031 application claims the followings (which read on the instant claimed method steps):

"A method of selecting a non-naturally occurring scaffold-based zinc finger polypeptide comprising more than three zinc fingers, that binds to a sequence of interest, comprising:

a) incubating primary libraries with target site constructs under conditions sufficient to form first binding complexes, wherein the primary libraries comprise scaffold-based zinc finger polypeptides having one variable finger and at least one anchor finger having, and wherein the target site construct has one subsite with a sequence identical to a subsite of the sequence of interest, and one or more subsites with sequences to which the anchor " finger(s) bind. b) isolating pools comprising nucleic acid sequences encoding polypeptides, wherein said polypeptides comprise the first binding complexes; c) recombining the pools to produce a secondary library; d) incubating the secondary library with the sequence ofinterest under conditions sufficient to form a second binding complex; and e) isolat!ng nucleic acid sequences encoding non-naturally occurring scaffold- based zinc finger polypeptides, wherein the scaffold-based zinc finger polypeptides comprise the second binding complexes."

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sue Liu whose telephone number is 571-272-5539. The examiner can normally be reached on M-F 9am-3pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low can be reached at 571-272-0951. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Sue Liu/
Primary Examiner, AU 1639
3/29/09